

Item 2. The Examiner refers to two sets of claims. One which was originally filed with the PCT application and the second which were filed as amended. The Examiner is correct in presuming that the second set of claims which are the amended claims are the proper claims to be examined. The amended claims were received by the International Bureau on May 24, 1999 and includes claims 1-10. A new claim 11 has been added to clarify the scope of claim 9.

Item 3. The Examiner objects to the specification. On page 7 the formula should read  $(R'O)_2P(NR^2)_2$  and replacement page 7 is enclosed for filing in this application.

Page 8. The definition of  $X=Z$  should be (divalent) and the obvious typographical error is corrected on the enclosed replacement page 8.

Regarding the Examiner's question pertaining pyridine and morpholine, note that the reactant is  $NH_2$  plus the cation.

Item 4. No comment required.

Item 5. Applicants have reviewed your questions and report that both phosphate and sodium phosphate are correct. They also point out that the reason the examiner could not locate "trans-combretastatin A-4" in the outline search is that it is a totally new compound and that "combretastatin A-4" is only a cis-isomer. Further, applicants are not claiming to prepare a "racemic mixture" but rather a mixture of geometric isomers (cis and trans).

Further, in claim 1, the Examiner questions the location of the protective groups. The protective groups are on **both** the combretastatin A-4 ring **and** on the phosphite ester.

Regarding the "yield" in claim 1, the process creates all three products. It is believed that claim 1 as amended will resolve the Examiner's confusion. If not, please let me know.

Regarding the Examiner's question directed to claim 2, the applicants report that "/" means that the solvent for the dibenzyl phosphine is limited to "carbon tetrachloride".

Next the Examiner questions the language of claim 5. The claim is written to show the X attached to the combretastatin molecule is as intended.

Applicant has reviewed the Examiner's other criticism in view of 35 USC §112 and it is believed that the several objections have been overcome. If the Examiner still believes there are problems to address, she is cordially invited to call the undersigned counsel with her observations.

\* \* \*

Claim 9 stands rejected under §102 as anticipated by Rathbone, Pettit and Pettit. Applicant has divided claim 9 into claims 9 and 11. Applicant submits that this amendment obviates the bases for this rejection, which can therefore be withdrawn.

In the interest of clarity, the entire non-compliant amendment has been resubmitted with the compliant documents included.

In view of the foregoing, it is respectfully submitted that all of the Examiner's objections/rejections have been obviated/traversed and can be withdrawn, that claims can also be noted allowed, and that this application can be passed to issue. Early action to this end is respectfully requested and earnestly urged.

Respectfully submitted,



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April 18, 2002  
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box non-fee Amendment, Washington, D.C. 20231 on the date indicated below.

April 18, 2002

Candace C. Bloch  
Candace C. Bloch

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please insert the following replacement paragraph in the Specification.

Page 1, line 1,

---This Application is based on United States Provisional Applications S/N 60/071,070, filed January 9, 1998, and 60/111,581, filed December 1998, and is the national phase of PCT Serial Number PCT/US99/00419, filed January 8, 1999, which was assigned International Publication Number WO 99/35150.--

Page 7, in the diagram in immediate superposition to the lower arrow, kindly cancel “(R'O)<sub>2</sub>PN<sup>2</sup>” and substitute ---(R'O)<sub>2</sub>P(NR<sup>2</sup>)<sub>2</sub>---;

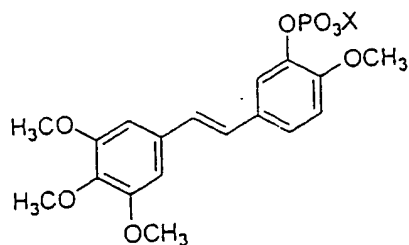
Page 8, line 22, cancel “(divavalent)” and substitute (divalent)

In the Claims

Kindly amend the claims as follows:

9.(Amended) [Combretastatin A-4 metal and ammonium phosphate prodrugs, and trans]

Trans-combretastatin A-4 prodrugs having the structure

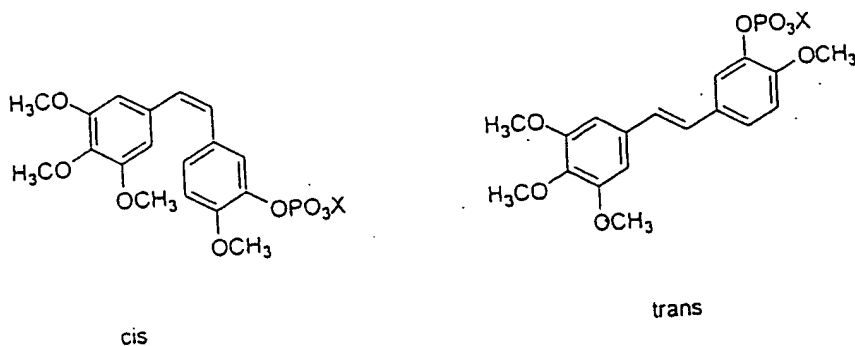


trans

wherein [Y] X is selected from the group consisting of cesium, calcium, lithium, magnesium, manganese, sodium, potassium, zinc, imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, and verapamil.

10. The method of claim 1 in which the ultimate product is recrystallized.

11. Combretastatin A-4 metal and ammonium phosphate prodrugs having the structure:



wherein X is selected from the group consisting of cesium, calcium, lithium, magnesium, manganese, zinc, imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, and verapamil.